

to the biological function of the lineage committed human cells that are cultured in a static culture; and wherein the lineage committed human cells are more differentiated than human stem and progenitor cells.

see p1021

see p 7 ll 4-7
p 9 ll 5-6

B2

42. (Amended) The method of claim 38, wherein the human lineage committed cells comprise hematopoietic cells, mesenchymal cells, keratinocytes, fibroblasts, hepatocytes, neural cells, epithelial cells, lymphocytes, osteoblasts or human osteoclasts.

Please add the following claims:

B3

48. (New) The method of claim 38, wherein the culture medium is replaced continuously.

don't all
of the CD34+
cells differentiate
eventually?

REMARKS

Claims 6-12, 38-45, 47, and 48 are active in the present application. Support for Claim 48 is found in Claim 9. Support for the amendment to Claim 38 is found on page 6, lines 17 through page 7, line 9 and page 9, lines 9-20. No new matter is believed to have been added by these amendments.

Applicants wish to thank Examiner Saunders for the courteous discussion granted to Applicants' undersigned representative on March 4, 2002. During this discussion, the undersigned noted that the cited prior art references of Emerson and Freedman do not disclose or teach culturing the lineage committed human cells as defined in the present claims. The Examiner indicated he would favorably reconsider his position upon filing the

present response. Accordingly, in view of the foregoing amendments and the following remarks, favorable reconsideration and allowance of all pending claims is requested.

The present invention provides the culturing of lineage committed human cells by replacing a liquid culture medium under which condition the lineage committed human cells have enhanced biological function. Such biological functions are discussed on pages 11-12 of the present specification. This method is neither disclosed or suggested by the prior art references cited in the Official Action (Paper No. 23).

The rejection of Claims 8-12, 38-40, 42-43 and 46-47 under 35 U.S.C. §102(b) over Emerson et al (U.S. Patent No. 5,437,994) is respectfully traversed.

Emerson et al disclose the culturing of human stem or progenitor cell (e.g., stromal cells) by a method wherein a liquid culture medium is replaced or perfused at a specified rate (see col. 4, lines 39 through col. 5, line 9). However, Emerson et al do not disclose or suggest the present method whereby lineage committed human cells are cultured to enhance the biological function of those cells.

Accordingly, the present claims are not anticipated by the disclosure of Emerson et al and as such, withdrawal of this ground of rejection is respectfully requested.

The rejection of Claims 6, 9-12, 38-39, 41-42 and 44-46 under 35 U.S.C. §102(b) over Freedman et al is respectfully traversed.

Freedman et al provides methods of culturing tumor infiltrating lymphocytes (TIL) to expand the number of cells (see page 46, col. 2, second paragraph: "We have developed and reported here a four-step method for expanding TIL. . ."). The four-step method of Freedman is set forth on page 147, col. 2 through page 150, col. 1. However, Freedman et al do not disclose the conditions for culturing lineage committed cells nor the recognition that in so

culturing such cells, one could obtain lineage committed cells with enhanced biological function. This is particularly true in light of the Freedman disclosure for expansion of the number of cells.

The Examiner has alleged that the Freedman disclosure of expansion of cell numbers is the same as the "enhanced replicative potential" as recited in Claims 12, 39 and 46 (see page 5 of the Official Action). This is incorrect.

Expansion is the multiplication of the number of cells present whereas replicative potential means:

... product cells have a greater ability to produce more cells as compared to the cells that were used at the beginning of the culturing. . . the product cells of the present invention have a greater ability to replicate or further differentiate to the desired cell type as compared to the same cells which have been cultured at low densities in a static culture (page 9, lines 15-19 of the present specification).

not a number

Thus, in one aspect of such enhanced replicative potential, the cells obtained in accordance with the present method are more capable of replication even after they are moved from the culture, e.g., upon transplantation into patient, compared to cells which are simply expanded (as in the Freedman reference).

The Examiner further alleges that TIL that are obtained by the method Freedman also have enhanced biological function based on page 157, cols. 1-2 of Freedman et al: "TIL expanded in the ACCS (four steps), from patient #028 and #029 exhibited preferential killing of autologous tumor cells." However, continuing to read from Freedman clarifies this observation: the effect was "due to disappearance or significant reduction of the nonspecific cytotoxicity during the four step of the expansion (ACCS)." Therefore, the effect observed

*but see specification page 11.
disappearance of nonspecific
cytotoxicity is consistent with
claim read in light of disclos*

in Freedman et al is **not** an enhancement of a biological function of the cells themselves, but rather a reduction or loss of some toxic side effect normally associated with TIL.

In view of the foregoing, the present claims are not anticipated by the disclosure of Freedman et al and as such, withdrawal of this ground of rejection is respectfully requested.

The rejection of Claims 6-12 and 38-47 under 35 U.S.C. §112, second paragraph is believed to have been obviated by amendment.

The objection to Claims 9, 12, 42 and 46 is believed to have been obviated by amendment.

Applicants submit the present application is now ready for allowance. Early notification of such allowance is earnestly solicited.

Respectfully submitted,

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IN THE CLAIMS

Please amend the claims as follows:

38. (Amended) A method for obtaining lineage committed human cells with enhanced biological function comprising culturing lineage committed human cells under physiologically acceptable liquid culture conditions, said conditions including replacement of ~~the~~ a liquid culture medium at a rate and for a time sufficient to obtain human lineage committed cells with enhanced biological function, wherein said enhanced biological function is relative to the biological function of the lineage committed human cells that are cultured in a static culture; and wherein the lineage committed human cells are more differentiated than human stem and progenitor cells.

42. (Amended) The method of claim 38, wherein the human lineage committed cells comprise hematopoietic cells, mesenchymal cells, keratinocytes, fibroblasts, [heptacytes] hepatocytes, neural cells, epithelial cells, lymphocytes, osteoblasts or human osteoclasts.